Peer Review File
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Comment 1: Lines 288-195: selection for Teliso-V is based on MET-overexpression, not METamp (as noted in ALK+ resistance), therefore I suggest adding a reference here that links MET-OE with METamp (e.g. https://pubmed.ncbi.nlm.nih.gov/28838386/).

Reply 1: We thank the reviewer for this comment and agree with importance of pointing out the correlation between MET-overexpression and amplification. We have added the suggested reference.

Changes in the text: “telisotuzumab may have activity in this setting given the correlation between MET amplification and overexpression (56).” These changes can be found on page 8, lines 323-324 of the revised manuscript with tracked changes.

Comment 2: Lines 307-315: T-DXd is not directly relevant here, please consider omitting this (except if you wish to discuss HER2mut/HER2OE as a resistance mechanism, which is not the case in the current version of the manuscript)

Reply 2: We thank the reviewer for comment on relevance of T-DXd in the discussion. We have changed to phrasing to reflect discussion on resistance mediated by *HER2* amplification or HER2 overexpression.

Changes in the text: “this drug may be an attractive option to overcome resistance mediated by *HER2* amplification or HER2 overexpression (61).” These changes can be found on page 9, lines 344-345 of the revised manuscript with tracked changes

Comment 3: Lines 138-144 (and Table 1): the authors mention only the ongoing SUPRESS-NSCLC trial with no results yet, but another trial (actually the very first randomized OPD trial in NSCLC with readout) has already delivered positive results: CURB trial presented in ASTRO Dec 2021 (https://www.sciencedirect.com/science/article/pii/S0360301621028133). There are also other ongoing similar trials (HALT NCT03256981 and STOP NCT02756793). The main text and/or Table 1 should be improved accordingly.

Reply 3: We thank the reviewer for this important suggested revision and apologize for the oversight in our initial submission. We appreciate information on these trials, which have now been included in the text and table as appropriate.

Changes in Text: (page 4, lines 146-159, of the revised text with tracked changes)

Recently reported data from the Consolidative Use of Radiotherapy to Block (CURB) trial showed that disease control can be improved with local therapy to progressive lesions alone in oligoprogressive disease (28). CURB, a randomized phase II trial, enrolled patients with oligoprogressive lesions (<=5) amenable to SBRT in patients with metastatic cancers of the lung and breast. Among patients with NSCLC, median PFS was improved with SBRT compared to standard of

care (44 weeks vs. 9 weeks, p=0.004). However, the majority (86%) of patients in this study did not harbor an actionable mutation within their tumor. Regardless, this study demonstrated the importance of local therapy in oligoprogressive disease. To that end, other ongoing studies including the phase II trial SUPPRESS-NSCLC (NCT04405401), phase II HALT trial (NCT03256981) and phase II STOP trial (NCT02756793) will provide further evidence of the role of SBRT in oligoprogressive disease (Table 1). The HALT trial planned to enroll patients with actionable mutation positive advanced NSCLC with oligoprogressive disease following initial response to a TKI, with the aim to study whether the use of SBRT to ≤ 3 sites of oligoprogressive disease with continuation of TKI improves PFS compared with continuation of TKI alone.

Comment 4: Lines 360-370 (adjuvant+neoadjuvant): the authors mention just one ongoing trial (LCMC4 = NCT04712877), but there is e.g. also the ALINA trial (NCT03456076) and also the large multiarm trial NCT04302025.

Reply 4: We appreciate information on these trials, which have now been included in the text, as described below, and in Table 1.

Changes in Text: (page 10, lines 406 to 413 of the revised text with tracked changes)

"NAUTIKA1 (NCT04302025) also aims to study neoadjuvant and adjuvant therapies in biomarker-selected populations with resectable NSCLC. The ALK cohort within NAUTIKA1 will receive up to 8 weeks of neoadjuvant alectinib treatment followed by surgical resection and subsequent adjuvant chemotherapy and alectinib (for up to 2 years), with the primary endpoint of assessing major pathologic response. Finally, ALINA (NCT03456076) is a phase III study of alectinib versus chemotherapy as adjuvant therapy in patients with stage IB–IIIA ALK-positive NSCLC. The primary endpoint in this trial is disease-free survival per investigator; with OS, safety, and pharmacokinetics as secondary endpoints."

Comment 5: Lines 384-391: the authors discuss only CML, but there are also published promising data on the use of ctDNA assays (targeted NGS and/or shallow WGS) to monitor ALK+ NSCLC and identify disease progression/characterize molecular evolution earlier than with radiologic restaging and tissue rebiopsies, one good example being PMID 34876698.

Reply 5: We thank the reviewer for their comments. We appreciate their effort to improve our manuscript with additional supporting data. We have added the following text and the suggested reference by the reviewer.

Changes in Text: We have added on page 11, lines 430-432 to the main text with tracked changes.

"Similarly, utility of ctDNA in ALK-positive NSCLC has been demonstrated for identifying genomic alterations that may mediate TKI resistance and for longitudinal monitoring to predict disease progression prior to radiographic evidence of disease progression (77,78)."

Comment 6: Lines 394-406 and ref. 72-76: there must be a misunderstanding here. The cited ref. 74

actually showed in a randomized comparison the opposite of what the authors argue for: that intermittent TKI therapy was much worse compared to continuous TKI therapy in terms of PFS (contrary to the preclinical results and the hypothesis that the study intended to prove; NB these misleading preclinical data had been published e.g. in PMID 23302800 and PMID 25600339 earlier, at a similar time (2015) as the similar preclinical data cited as ref. 72 by the authors to support their argumentation in this section). Ref. 73 does not compare intermittent to continuous dosing. Ref. 75 only lists retrospective evidence that intermittent dosing is feasible in RCC (without detecteble disadvantage in these retrospective analyses, but also no claim of superiority). Ref. 76 refers to the phenomenon of clonal tide (KRASmut = EGFRAb-resistant clones tiding back and forth under different lines of therapy and associated with the benefit from EGFRAb), which is also a different situation than the putative TKI-addiction and improvement of TKI benefit through TKI withdrawal proposed by the authors here. Thus, the results presented in ref 72-76 are neither "similar"/consistent with each other, as stated in the current version of the manuscript, nor promising in terms of pausing ALK TKI treatment in ALK+ NSCLC patients with good response in order to prolong survival. There are no data to support pausing ALK TKI in a responsing ALK+ NSCLC patient currently, and actually seveal lines of evidence suggest that this could turn out to be catastrophic. I suggest that the entire part of lines 396-406 is modified.

Reply 6: Thank you for the comment. We agree with the reviewers comment on the conflicting results and have deleted the section titled “intermittent therapy” in the updated manuscript.

Comment 7: Line 87: 5 ALK TKI are approved by the FDA/EMA, however in global terms there is also a 6th compound with a phase 3 study which is approved (ensartinib).

Reply 7: We thank the reviewer for this comment. We have provided clarification on this point by including the agencies approving ALK TKIs, with specific mention of ensartinib approval in China.

Changes to the text: We have added on page 3, lines 92-96 to the main text with tracked changes.

“There are currently 5 TKIs approved by the U.S Food and Drug Administration and European Medicines Agency for the treatment of patients with ALK-positive lung cancer in the advanced / metastatic disease. Ensartinib [a 2nd generation ALK TKI] is also currently approved in China (13).”

Comment 8: Different subsections in the manuscript are organized with somewhat strange subtitles

Reply 8: We are grateful for the reviewer’s kind comments and support. We have now added numbers in front of major sections/subsections for easier readability.

Changes in Text: “Management of Oligoprogression” was changed to “1. Management of Oligoprogression”, “Management of Systemic Progression” changed to “2. Management of Systemic Progression” and further subsections are numbered, 2.1, 2.2, etc. “Other Potential Strategies to Maximize Response to ALK TKI Therapy” changed to “3. Other Potential Strategies to Maximize Response to ALK TKI Therapy.”